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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,391	01/07/2002	Jamey D. Marth	19452A-000320US	7913

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,391	MARTH ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office action is in response to the communication filed 11-28-05.

Claims 36-49 are pending in the instant application.

Response to Arguments/Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 36-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of systemic C2 GlcNAc T^{Δ} or conditional C2 GlcNAc T^{F} homozygous mice using Cre-loxP recombination, whereby a deficiency of C2 GlcNAc transferase activity and a deficiency of core 2 O-glycan synthesis were observed in isolated null mouse splenocytes, does not reasonably provide enablement for methods of inhibiting inflammatory responses in a mammal, or for methods of modulating binding of a first myeloid cell to a second myeloid cell or to an endothelial cell in an organism comprising the administration of compounds that are analogs of core 2 GlcNAc transferase in an organism for the reasons of record set forth in the Office action mailed 8-24-05 and for the reasons set forth below.

Applicant's arguments filed 11-28-05 have been fully considered but they are not persuasive. Applicant argues that the references cited in the prior Office action(s) are not relevant to the enablement issues of the instant claims because the previously cited references address the limited delivery of adequate concentrations of molecules such

as nucleic acid molecules and/or polypeptides to target cells in vivo, and, in contrast, the instant claims are drawn to methods of treatment involving the delivery of substrate analogs of C2GlcNAc transferase. Applicant argues further that the delivery of the substrate analogs encompassed by the genus claimed passively diffuse through a target cell's membrane, and that the permeability of small molecular weight compounds can be predicted using the model set forth by Camenisch et al, which predictions are based on the candidate molecule's lipophilicity, ionization state and molecular size. Applicant asserts further that, because of the ability to passively diffuse through target cell membranes, in vitro cell based assays are predictive of in vivo delivery (and hence efficacy). Applicant additionally asserts that some substrate analogs of glycosyl transferases have been used successfully in vivo for antibiotic and antibacterial agents, indicating the ability of such analogs to successfully diffuse through the cell membrane and still readily bind to the active site of the target enzyme.

Applicant is correct that Camenisch sets forth a model for predicting the passive diffusion of small molecules into cells based on the candidate molecule's lipophilicity, ionization state and molecular size. But, contrary to Applicant's assertions, the correlation between the ability to predict the passive diffusion of a molecule under the controlled in vitro conditions set forth in the teachings of Camenisch, and the ability to mimic these conditions in vivo is lacking in the prior art and in the instant specification. The lack of predictability of efficacy (*e.g.* in extrapolating from in vitro conditions to those obtained in vivo) - and which are illustrated in the references previously cited and address the use of small nucleic acid molecules or polypeptides - also exists for other

small molecules, whether the inhibitory molecules require transport mechanisms or are taken up by passive diffusion by the target cells. Furthermore, the ability to provide adequate delivery of the instantly claimed molecules to the desired subcellular organelles, whereby adequate inhibition of glycosyl transferase activity is obtained, is still a highly unpredictable endeavor in vivo. The unpredictability lies in determining whether effective inhibitor concentrations can be obtained in vivo to inhibit the target enzyme, following administration of the drug candidate. The phenotypes achieved in an ablated model represent a model response when a gene has already been ablated. But the question to be answered is whether any proposed inhibitors can provide treatment effects upon administration in vivo.

The teachings of Camenisch provide no correlation with small molecule delivery to target cells in vivo, nor do they provide any correlation between the in vitro permeability of a small molecule and the ability to provide treatment effects. Camenisch merely provides a comparison between a small molecule's ability to permeate a monolayer of cultured cells under very controlled conditions in vitro, with that molecule's distribution coefficient in 1-octanol/water (and its molecular weight).

The ability to provide antibiotic effects (*e.g.* providing toxic effects to bacterial cells, as asserted by Applicant) using glycosyltransferase analogs is not representative or correlative of the ability to provide anti-inflammatory effects in vivo upon administration of core 2 GlcNAc transferase substrate analogs to mammalian target cells. The concentration requirements and delivery issues involving mammalian target cells (and the requisite subcellular organelles) are different than those involving target

bacterial cells. In addition, the inhibition of one glycosyl transferase using one inhibitor is not necessarily predictive or correlative of the ability to inhibit a different target enzyme using a different inhibitor. In vivo treatment comprising administration of the various members of the instantly claimed genus requires undue experimentation beyond that taught in the instant disclosure, and beyond that taught in the art. For these reasons, the instant rejection for lacking enablement is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the

Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
2-19-06